2. RELEVANCE TO PUBLIC HEALTH

2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO DICHLOROBENZENES IN THE UNITED STATES

Dichlorobenzenes (DCBs) are chlorinated aromatic compounds that have three isomeric forms. 1,2-DCB is a colorless to pale yellow liquid used primarily as a precursor for 3,4-dichloroaniline herbicides. 1,3-DCB is a colorless liquid used in the production of various herbicides, insecticides, pharmaceuticals, and dyes. 1,4-DCB, the most commercially important dichlorobenzene isomer, is a volatile colorless to white crystalline material with a mothball-like, penetrating odor. It is used as a deodorant for restrooms, for moth control, and in the production of polyphenylene sulfide (PPS) resin.

DCBs are not known to occur naturally in the environment. The primary sources of 1,4-DCB of industrial or commercial origin in the environment are releases from space deodorants and moth repellants into the atmosphere. 1,4-DCB might also be released into water through waste water streams and landfill leachate and to soil through sewage sludge application, disposal of industrial waste, and atmospheric deposition. 1,2- and 1,3-DCBs are expected to be released to the environment during their use in herbicide production or during the use of other products containing these isomers. 1,2-DCB is produced in large quantities as a by-product during the production of 1,4-DCB and can be released into the environment during the disposal of unused supplies.

1,2-, 1,3-, and 1,4-DCB have similar physical and chemical properties, and consequently are expected to have similar environmental fates. DCBs will exist predominantly in the vapor-phase in the atmosphere. They are degraded in the atmosphere by reaction with hydroxyl radicals, with atmospheric lifetimes (theoretically calculated) of about 1 month. The detection of these chemicals in rainwater suggests that atmospheric removal via washout is possible. Depending on soil type, DCBs are expected to be moderately mobile in soil and to volatilize from surface water and soil surfaces to the atmosphere. Volatilization, sorption, biodegradation, and bioaccumulation are likely to be competing processes, with the dominant fate being determined by local environmental conditions.

DCB concentrations in soil, water, and food are generally low in comparison to concentrations in air, indicating that exposure of the general population to DCBs is predominantly by inhalation. Individuals are more likely to be exposed to 1,4-DCB than to the other isomers due to the widespread use of the

1,4-isomer in deodorant and moth repellent products. Measured DCB concentrations in ambient outdoor air generally range from 0.01 to 0.1 ppb for 1,2-DCB, from 0.001 to 0.1 ppb for 1,3-DCB, and from 0.01 to 1 ppb for 1,4-DCB. The average daily adult intakes of 1,2-, 1,3-, and 1,4-DCB from ambient air have been estimated to be about 1.8, 0.8, and 35 μg/day, respectively. The heavy use of products containing 1,4-DCB in homes and other buildings has resulted in higher concentrations of this substance in indoor air compared to concentrations in outdoor air. Measured 1,4-DCB concentrations in indoor air generally range from 0.1 ppb to 100 ppb. Indoor inhalation exposure to 1,2- or 1,3-DCB is not expected to be important since these substances are not used in household and consumer products to the extent of 1,4-DCB. 1,2- and 1,4-DCB have been detected in adipose tissue at concentrations ranging from <0.1 to 38 ppb and from 0.2 to 500 ppb, respectively. 1,4-DCB has been detected in blood samples at concentrations ranging from below 0.04 to 45 ppb, while measured 1,2-DCB concentrations in blood are below 3 ppb.

Children can be exposed to DCBs prenatally, as indicated by the detection of all three isomers in placenta samples, as well as through breast feeding. 1,2-DCB concentrations measured in whole human milk range from 3 to 29 ppb. 1,3- and 1,4-DCB were detected together in whole human milk with mean and maximum concentrations of 6 and 75 ppb, respectively. These isomers were detected in milkfat samples at a mean concentration of 161 ppb and a maximum concentration of 4,180 ppb. 1,2-, 1,3-, and 1,4-DCB measured separately in whole human milk samples had concentrations of 9, <5, and 25 ppb, respectively, while the milk fat of these samples contained 230 ppb of 1,2-DCB and 640 ppb of 1,4-DCB. Children and adults are perhaps at equal risk for exposure to 1,4-DCB since there is no evidence to indicate that children are likely to be exposed to lower amounts of 1,4-DCB from everyday living. While actual exposure reports are limited to a small number of case reports, available evidence suggests that children may be exposed to 1,4-DCB if they eat or play with moth balls or toilet deodorizers.

As seen in the exposure monitoring data, 1,3- and 1,4-DCB concentrations are sometimes reported together as a single value. This is most likely because 1,3- and 1,4-DCB co-elute on many GC columns such that their individual concentrations cannot be distinguished from each other. Based on the production volumes of these isomers, it is expected that concentrations reported for a combination of 1,3- and 1,4-DCB almost entirely represent the 1,4- isomer.

Occupational exposure to DCBs is expected to occur through inhalation and dermal contact with these substances during their formulation and use. Other people at risk for high exposure to DCBs include those living near sites where DCBs are produced, used, or disposed. People living or working near industrial facilities or hazardous waste sites with higher than average levels of DCBs in the air also would have the potential for above-normal exposures. Individuals using space deodorants (air fresheners), toilet block deodorants, or moth repellents (moth balls or crystals) containing 1,4-DCB in their homes have the potential for high exposure to this compound.

2.2 SUMMARY OF HEALTH EFFECTS

1,2-Dichlorobenzene. 1,2-DCB is quickly and extensively absorbed through both the gastrointestinal tract and the respiratory tract; studies measuring the absorption of 1,2-DCB following dermal exposure are not available. Following absorption, 1,2-DCB is distributed throughout the body, but tends to be found in greatest levels in the fat, kidney, and liver. 1,2-DCB is initially metabolized by cytochrome P-450 enzymes, specifically P4502E1, to an active epoxide followed by hydrolysis to 2,3-dichlorophenol or 3,4-dichlorophenol. The dichlorophenols may be further oxidized or, more often, be conjugated to glutathione, sulfate, or to form the glucuronide; conjugation occurs extensively, with virtually no unconjugated metabolites reported in the available studies. Metabolism is believed to occur mainly in the liver, but may occur at lower levels in other tissues, such as the kidney or lung. Elimination of 1,2-DCB from the body is rapid, with the majority of a single dose being removed within the first 75 hours postexposure; elimination occurs primarily in the urine as metabolites.

The liver is the primary target of animals orally exposed to 1,2-DCB, generally resulting in centrilobular damage. However, the acute data are inconsistent, with some studies indicating that short-term exposure of rats to as little as 455 mg/kg/day results in severe liver damage, while others reported no hepatic histopathologic changes in rats exposed to up to 1,000 mg/kg/day. Unlike the acute data, the intermediate and chronic data very clearly identify the liver as the most sensitive target of oral 1,2-DCB exposure. Several intermediate-duration studies in rats and mice have reported changes in liver weight and histology, including cloudy swelling of the liver and centrilobular degeneration, beginning at concentrations of 188–400 mg/kg/day. A chronic study in rats and mice found no nonneoplastic liver effects in either sex of either species, even at exposures up to 120 mg/kg/day, suggesting that the nonneoplastic hepatic effects of 1,2-DCB might have a threshold between 120 and 188 mg/kg/day.

Industrial hygiene studies have not reported nasal or eye irritation in humans exposed to 50 ppm of 1,2-DCB or less. However, exposure of humans to 100 ppm resulted in irritation of the eyes and respiratory passages. In mice exposed to 64 ppm or greater of 1,2-DCB for 4, 9, or 14 days, histologic alterations of the olfactory epithelium, but not the respiratory epithelium of the nasal cavity or in the trachea or lungs, were reported; the lesions decreased in severity with increasing exposure duration, suggesting that repair occurred.

Data on the possible effects of 1,2-DCB on reproductive or developmental end points in humans are not available. Animal studies by both the oral and inhalation routes of exposure have failed to find effects of 1,2-DCB on reproductive organs or indices of reproduction. Similarly, the limited data available suggest that 1,2-DCB exposure does not have a significant effect on development of the fetus.

Data on the possible carcinogenic effects of 1,2-DCB in humans are not available. Exposure to 1,2-DCB by the oral route has not been shown to cause an increase in tumor formation following lifetime exposure in rats or mice. The potential carcinogenic effects of 1,2-DCB by other routes of exposure have not been evaluated.

Hepatic Effects. Data on the hepatic effects of 1,2-DCB in exposed humans are not available for any exposure route. The liver is the primary target of animals orally exposed to 1,2-DCB, generally resulting in centrilobular damage in acute- and subchronic-duration studies. A single exposure to 1,500 mg/kg in rats resulted in lethal central necrosis. In rats exposed to 455 mg/kg/day for 15 days, severe liver damage, characterized by intense necrosis and fatty changes, and porphyria were reported. Similarly, rats exposed to 300 mg/kg/day for 10 days showed hepatic necrosis of slight severity and increased serum alanine aminotransferase (ALT). However, an acute (14-day) study by the National Toxicology Program showed no hepatic effects in male or female rats given as high as 500 or 1,000 mg/kg/day for 14 consecutive days. Centrilobular effects similar to those reported in the acute studies were reported in several subchronic studies in rats and mice and occurred in rats exposed to 188 mg/kg/day for 138 doses, in rats exposed to 400 mg/kg/day for 90 days, in rats exposed to 250 mg/kg/day or greater for 13 weeks, and in mice exposed to 250 mg/kg/day for 13 weeks. A chronic study in rats and mice found no nonneoplastic liver effects in either sex of either species, even at exposures up to 120 mg/kg/day, suggesting that the nonneoplastic hepatic effects of 1,2-DCB may have a threshold, which might fall between 120 and 188 mg/kg/day.

Respiratory Tract Effects. Periodic industrial hygiene surveys and medical examinations were conducted in a plant where an unreported number of men were exposed to 1,2-DCB at an average level of 15 ppm (range, 1–44 ppm) for an unreported duration; no nasal or eye irritation was attributable to exposure. Additionally, the study author noted that the researchers detected 1,2-DCB odor at a concentration of 50 ppm without eye or nasal irritation during repeated vapor inhalation experiments on animals. An earlier source reported that occupational exposure to 100 ppm of 1,2-DCB caused irritation of the eyes and respiratory passages of exposed humans. Data on the effects of 1,2-DCB on the respiratory tract in humans following oral or dermal exposure are not available.

In male Swiss OF1 mice exposed to 1,2-DCB in actual mean concentrations of 0, 64, or 163 ppm (0, 385, or 980 mg/m^3) for 6 hours/day, 5 days/week for 4, 9, or 14 days, histopathologic lesions were observed in the olfactory epithelium of the nasal cavity at ≥64 ppm. The olfactory epithelial lesions were graded as very severe following the 4-day exposure and moderate after the 14-day exposure, indicating to the study authors that repair may occur despite continued exposure. The more severe cases were characterized by a complete loss of olfactory epithelium, which left only the partially denuded basement membrane. No histological alterations were observed in the respiratory epithelium of the nasal cavity, or in the trachea or lungs. No effects on respiratory tract tissues were reported in subchronic or chronic oral studies in animals; however, in most cases, histologic evaluation of the nasal tissues was not done.

1,3-Dichlorobenzene. Data on the absorption of 1,3-DCB in humans and animals are not available for any route of exposure; however, absorption of the compound can be inferred from studies that have detected 1,3-DCB or metabolites in the breast milk, blood, and fat of humans and in the bile and urine of exposed animals. Distribution is believed to be similar to the other DCB isomers, but data demonstrating this are not currently available. Similar to the other DCB isomers, 1,3-DCB is initially metabolized by cytochrome P-450 enzymes, followed by extensive conjugation, primarily to glutathione, has been reported. 1,3-DCB is eliminated mainly in the urine, similar to the other DCB isomers.

Studies on the toxic effects of 1,3-DCB in humans are not available. No studies evaluating the toxicity of 1,3-DCB following dermal or inhalation exposure in animals were located.

The most sensitive adverse health effects identified by the available animal studies of 1,3-DCB were effects on the endocrine system. Exposure of male rats to ≥9 mg/kg/day, or females to ≥37 mg/kg/day, for 90 days resulted in reduced follicular colloidal density in the thyroid, and cytoplasmic vacuolization of the pars distalis of the pituitary. The incidence of both the thyroid and pituitary lesions were dose-related, and increased in severity with increasing dose level. Other effects in this study included increases in serum cholesterol and calcium, which the study authors suggested may be related to the effects seen on the thyroid, pituitary, or other endocrine organs.

Effects on the liver are another potentially important effect of 1,3-DCB exposure. Treatment of rats with up to 735 mg/kg/day by gavage resulted in hepatic centrilobular degeneration, beginning at 368 mg/kg/day; both incidence and severity increased with increasing dose. Similarly, exposure of rats to 9–588 mg/kg/day by gavage for 90 days resulted in increased relative liver weight and histological alterations of the liver (including inflammation, hepatocellular alterations, and hepatocellular necrosis) at doses of ≥147 mg/kg/day. Other statistically significant liver-associated effects included significantly increased serum aminotransferase (AST) levels (90–100% higher than controls) in males at ≥9 mg/kg/day and females at ≥37 mg/kg/day. Serum lactate dehydrogenase (LDH) levels were also reduced in males at ≥9 mg/kg/day, but the biological significance of a decrease in liver enzymes is unclear.

Reproductive function following exposure to 1,3-DCB has not been evaluated in humans or animals. This only available information on the developmental toxicity study of 1,3-DCB is from a gavage study reported without details as an abstract, which reported no treatment-related effects on development. Studies evaluating the possible carcinogenic effects of 1,3-DCB were not available in the examined literature.

Endocrine Effects. In a 90-day study in rats given 0, 9, 37, 147, or 588 mg/kg/day, the most sensitive reported effects were on the pituitary and thyroid glands. Histologically, depletion of colloid density in the thyroid, characterized by decreased follicular size with scant colloid and follicles lined by cells that were cuboidal to columnar, was increased in a dose-related manner in males exposed to ≥9 mg/kg/day, and in females exposed to ≥37 mg/kg/day. Similarly, the pituitary glands of males exposed to 1,3-DCB showed cytoplasmic vacuolization of the *pars distalis* in all exposed groups, but the incidence was statistically significant only in animals exposed to ≥147 mg/kg/day. Increases in serum cholesterol in males at ≥9 mg/kg/day and females at ≥37 mg/kg/day, and serum calcium in both sexes at ≥37 mg/kg/day were also believed by the authors to be related to effects on endocrine end points, possibly reflecting a disruption of hormonal feedback mechanisms, or target organ effects on the pituitary, hypothalamus, and/or other endocrine organs.

Hepatic Effects. In male and female rats exposed by gavage to up to 735 mg/kg/day for 10 days, hepatic effects included significantly increased relative liver weight in males at ≥147 mg/kg/day and females at ≥368 mg/kg/day, and altered histopathology at ≥368 mg/kg/day in both sexes. The main hepatic histological change was dose-related centrolobular hepatocellular degeneration, characterized by varying degrees of cytoplasmic vacuolization and swelling with intact membranes. Other hepatic alterations included hepatocellular necrosis that was sporadically noted in animals exposed to

≥147 mg/kg/day; this change was usually minimal to mild, and tended to increase in incidence and severity in males in a dose-related manner. In a 90-day study of 1,3-DCB toxicity, rats of both sexes were exposed by gavage to up to 588 mg/kg/day. Relative liver weights were increased in both sexes at ≥147 mg/kg/day. Dose-related increases in histological lesions, including inflammation, hepatocellular alterations, and hepatocellular necrosis were reported at doses of ≥147 mg/kg/day. Other statistically significant liver-associated effects included significantly increased serum AST levels (90–100% higher than controls) in males at ≥9 mg/kg/day and females at ≥37 mg/kg/day, but whether these changes were due to an effect on the liver or an endocrine effect is not clear. Serum LDH levels were also reduced in males at ≥9 mg/kg/day, but the biological significance of a decrease in liver enzymes is unclear.

1,4-Dichlorobenzene. Following inhalation or oral exposure, absorption of 1,4-DCB is rapid and complete. Data on the absorption of 1,4-DCB following dermal exposure are not available; however, absorption is believed to be very low, based on a very high (>6 g/kg) dermal LD_{50} for 1,4-DCB in rats, and on a lack of systemic effects in humans who held solid 1,4-DCB in their hands. Similar to the other dichlorobenzene isomers, 1,4-DCB is distributed throughout the body, but tends to be found in greatest levels in fat, liver, and kidney. Metabolism of 1,4-DCB is similar to that of 1,2-DCB, with an initial oxidation to an epoxide, followed by hydrolysis to 2,5-dichlorophenol. Extensive phase II metabolism occurs subsequently, with eliminated metabolites found mainly as the sulfate, glucuronide, or mercapturic acid. 1,4-DCB is eliminated almost exclusively in the urine, primarily as conjugates of 2,5-dichlorophenol.

Effects on the liver have been shown to be a sensitive end point following exposure of 1,4-DCB in humans and animals. In two human fatalities thought to be caused by 1,4-DCB, the subjects died of a massive hepatic necrosis. A 3-year-old who had been playing with 1,4-DCB crystals was admitted to the hospital displaying signs of jaundice, and recovered after a transfusion. Animal studies have reported increased liver weights, liver cell proliferation, vacuolated cytoplasm, hepatocellular hypertrophy, and hepatic portal inflammation following exposure to 1,4-DCB.

Inhaled 1,4-DCB has irritant effects, as demonstrated in a study of 58 workers who reported painful irritations of the nose after occupational exposures to 80–160 ppm. A chronic study in rats demonstrated histologic changes of the olfactory epithelium in female rats exposed to ≥75 ppm of 1,4-DCB.

Data on the effects of 1,4-DCB on reproductive end points in humans are not available. In the majority of oral and inhalation studies in animals, exposure to 1,4-DCB has not been demonstrated to produce treatment-related changes in reproductive tissues or on reproductive end points, with the notable exception of a 2-year inhalation study in rats that reported a mineralization of the testes at concentrations of ≥75 ppm.

A 21-year-old woman who had eaten 1–2 blocks of 1,4-DCB toilet freshener per week for the first 38 weeks of pregnancy gave birth to an apparently normal child. In rats orally exposed to 90 mg/kg/day throughout gestation, decreased pup weights at birth and increased occurrence of clinical signs in pups (dry, scaly skin and tail constriction) were reported; exposure to 270 mg/kg/day in the same study resulted in decreased offspring survival and decreased pup weight during weaning. Other studies of the developmental effects of 1,4-DCB have been negative, or have reported only mild anomalies (e.g., extra ribs in rodent bioassays).

Data on the carcinogenic effects of 1,4-DCB in humans are not available. 1,4-DCB has been shown to be carcinogenic in chronic animal studies by both the inhalation and oral routes. Following lifetime inhalation exposure, a dose-related increase in hepatic tumors was reported in mice of both sexes, but not in either sex of rats. Following lifetime oral exposure, hepatic tumors were increased in mice of both sexes, but not in either sex of rats; male rats exposed to 1,4-DCB developed renal tubular cell adenocarcinomas, but these are believed to be the result of interaction with $\alpha_{2\mu}$-globulin, a renal protein not present in humans. Data on the possible carcinogenic effects of 1,4-DCB following dermal exposure are not available.

Hepatic Effects. In two human fatalities believed to be caused by 1,4-DCB inhalation, the subjects died of a massive hepatic necrosis known as acute yellow atrophy of the liver; the inhaled concentration is not known. A 3-year-old boy who had been playing with crystals containing 1,4-DCB for 4–5 days was jaundiced with pale mucous membranes, indicative of liver damage; with transfusion, the child gradually improved.

Many animal studies by both the oral and inhalation routes have confirmed the liver as a sensitive target for 1,4-DCB toxicity. Inhaled exposure concentrations of 158–211 ppm, at exposure durations from 2 weeks to 7 months, resulted in increased liver weights, cloudy swelling of the liver, and, at higher exposure levels, centrilobular hypercellular hypertrophy and necrosis. Exposure to 538 ppm for 10 weeks, and throughout mating and gestation for females, resulted in hepatocellular hypertrophy and increased liver weights in both the parents (F_0 generation) and the offspring (F_1). In chronic inhalation studies in rats and mice, no effects were seen in either sex of either species at 75 ppm, but at 300 ppm, histological changes were seen in male mice, but not in female mice or in either sex of rats. Acute oral studies have demonstrated hepatic effects (increased liver weight) at concentrations as low as 300 mg/kg in rats, with higher concentrations resulting in increased liver cell proliferation and vacuolated and/or basophilic cytoplasm of centrilobular cells. Similar hepatic effects have been seen in mice exposed to 300 mg/kg/day for 1 week. In rats exposed to 1,4-DCB for 13 weeks, increased relative liver weight was seen at ≥75 mg/kg/day, with centrilobular hypertrophy present at 300 mg/kg/day, and necrosis reported at 1,200 mg/kg/day; studies in mice have reported similar effects. A 1-year study in male and female Beagle dogs reported increased liver weights, hepatocellular hypertrophy, pigment deposition, and hepatic portal inflammation after exposure to 50 or 75 mg/kg/day. In the only 2-year oral study of 1,4-DCB toxicity, no effects were seen in either sex of rats exposed to up to 300 mg/kg/day, while both sexes of mice showed significant, dose-related increases in hepatocellular degeneration, starting at 300 mg/kg/day.

Respiratory Effects. A case of pulmonary granulomatosis was reported to have occurred in a 53-year-old woman who for 12–15 years had been inhaling 1,4 DCB crystals that were scattered on a weekly basis on the carpets and furniture of her home. A lung biopsy revealed the presence of 1,4-DCB crystals with the surrounding lung parenchyma being distorted by fibrosis, thickening of the alveolar walls, and marked infiltrates of lymphocytes and mononuclear phagocytes. These effects are most likely related to the physical interaction of 1,4 DCB crystals (or any crystals when inhaled) with lung tissue, rather than to chemical toxicity. A study of 58 men occupationally exposed for 8 hours/day, 5 days/week, continually or intermittently, for 8 months to 25 years (average, 4.75 years) to 1,4 DCB found painful irritations of the nose at levels ranging from 80 to 160 ppm. At levels >160 ppm, the air was considered not breathable for unacclimated persons.

In a chronic inhalation study, male and female rats exposed to 490–499 ppm showed a small but significant increase in lung weight after 112 weeks of exposure; this response was not seen at study week 76 . The 112-week study did not evaluate nasal tissues. A later chronic inhalation study reported that in rats exposed to 1,4-DCB for 6 hours/day, 5 days/week for 2 years, an increased incidence of histological changes of the olfactory epithelium was seen in male rats exposed to 300 ppm, and in female rats exposed to 75 or 300 ppm. No changes were reported in the nasal epithelium of exposed mice. In rats treated with 1,200 or 1,500 mg/kg/day or greater by gavage for 13 weeks, epithelial necrosis of the nasal turbinates was reported; similar effects were not seen in mice exposed by gavage to up to 1,800 mg/kg/day, or in rats or mice exposed by gavage for 2 years to up to 600 mg/kg/day.

Renal Effects. Exposure of male rats to 1,4-DCB, but not female rats or either sex of mice, results in the development of renal lesions, characterized by cellular proliferation of the proximal tubules, formation of protein droplets in the renal tubular cells, increased kidney weight, tubular cell necrosis, and increased incidence of renal tumors. These have been shown to be the result of interaction with the protein $\alpha_{2\mu}$-globulin, a mechanism specific to male rats and not relevant to consideration of human exposures.

Developmental Effects. A 21-year-old woman who had eaten 1–2 blocks of 1,4-DCB toilet freshener per week for the first 38 weeks of pregnancy gave birth to an apparently normal child. In a 2-generation study of the effects of inhaled 1,4-DCB on reproduction and development, the number of pups that died during the perinatal period was increased, and the body weights at postnatal day 0 and 28 were significantly decreased, in animals exposed to 538 ppm; exposures to 66.3 or 211 ppm had no effect on developmental endpoints. In rabbits exposed to 300 ppm, but not those exposed to 800 ppm, there was a significant increase in the number of resorptions and the percentages of resorbed implantations per litter; the fact that the effect did not occur in rabbits exposed to a higher dose level suggests that it was not treatment-related. In a 2-generation oral study in rats, treatment with 90 mg/kg/day of 1,4-DCB resulted in increased mortality in the F_2 generation, decreased pup birth weight in the F_1 generation, and increased occurrence of clinical signs in pups (dry, scaly skin and tail constriction); exposure to 270 mg/kg/day in the same study resulted in decreased offspring survival and decreased pup weight during weaning of the F_1 and F_2 generations. Other evaluations of the developmental effects of 1,4-DCB following oral exposure have been negative.

2.3 MINIMAL RISK LEVELS

Inhalation MRLs

1,2-Dichlorobenzene. No MRL was derived for acute-duration inhalation exposure to 1,2-DCB due to insufficient data. A limited amount of information is available on the toxicity of acute inhalation exposure to 1,2-DCB. Workers who were exposed to concentrations ranging from 1 to 44 ppm (average 15 ppm) for unreported durations did not experience eye or nasal irritation and showed no changes in standard blood and urine indices, as shown by periodic occupational health examinations (Hollingsworth et al. 1958). 1,2-DCB also did not cause eye or nasal irritation in people exposed to approximately 50 ppm (researchers who were exposed during the conduct of inhalation studies in animals), although the odor was perceptible at this level (Hollingsworth et al. 1958). Occupational exposure to higher concentrations of 100 ppm 1,2-DCB was reported to be irritating to the eyes and respiratory passages (Elkins 1950). This limited information on irritation effects of 1,2-DCB in humans is consistent with histological findings of nasal olfactory epithelial lesions in mice exposed to 64 or 163 ppm of 1,2-DCB for 6 hours/day, 5 days/week for 4, 9, or 14 days (Zissu 1995). The olfactory epithelial lesions were graded as very severe following the 4-day exposure and moderate after the 14-day exposure, suggesting to the authors that some tissue repair might have occurred despite continued exposure. The more severe cases were characterized by a complete loss of olfactory epithelium, which left only the partially denuded basement membrane. No histological alterations were observed in the respiratory epithelium of the nasal cavity, or in the trachea or lungs. Nonrespiratory tissues were not evaluated in this study.

Acute systemic effects of inhaled 1,2-DCB include histopathology in the liver (marked centrilobular necrosis) and kidneys (cloudy swelling of tubular epithelium) of rats exposed to 977 ppm for 1 hour (Hollingsworth et al. 1958), but not to 539 ppm for 3 or 6.5 hours (Hollingsworth et al. 1958) or 322 ppm for 6 hours/day for 10 days (DuPont 1982). Maternal body weight gain was decreased in rats and rabbits that were exposed to 100, 200, or 400 ppm of 1,2-DCB for 6 hours/day on days 6–15 (rats) or 6–18 (rabbits) of gestation (Hayes et al. 1985). A maternal no-observed-adverse-effect level (NOAEL) is not identifiable because the effect occurred at all tested exposure levels. No prenatal developmental toxicity was observed in the rabbits. Skeletal variations (delayed ossification of cervical vertebral centra) occurred in fetuses of rats at 400 ppm, indicating that developmental effects occurred in rats at concentrations that also caused maternal toxicity. Based on these findings, a NOAEL of 200 ppm and a lowest-observed-adverse-effect level (LOAEL) of 400 ppm are identified for developmental toxicity.

The nasal histopathology findings in mice show that the upper respiratory tract is a sensitive target for acute inhalation exposure to 1,2-DCB, as serious olfactory lesions occurred at exposure concentrations below those that caused systemic or developmental effects in rats and rabbits. The 64 ppm serious LOAEL for nasal olfactory lesions precludes derivation of an acute inhalation MRL for 1,2-DCB because: (1) a NOAEL was not determined by Zissu (1995), (2) no other animal studies tested exposure levels below 100 ppm or evaluated the nasal cavity, and (3) it is consistent with limited reports indicating that occupational exposure to 100 ppm is irritating to the eyes and respiratory tract of humans (Elkins 1950; Hollingsworth et al. 1958).

No intermediate-duration inhalation MRL was derived for 1,2-DCB due to insufficient data. Information on the toxicity of intermediate-duration inhalation exposures to 1,2-DCB is limited to the findings of a multispecies subchronic study (Hollingsworth et al. 1958) and a 2-generation reproduction study in rats

(Bio/dynamics 1989). In the subchronic study, rats and guinea pigs were exposed to 49 or 93 ppm for 7 hours/day, 5 days/week for 6–7 months (Hollingsworth et al. 1958). Mice were similarly exposed to 49 ppm only, and rabbits and monkeys were similarly exposed to 93 ppm only, although the rabbit and monkey data are compromised by small numbers of animals (two rabbits/sex and two female monkeys). No compound-related histopathological or other changes occurred in any of the animals exposed to 49 ppm. The only remarkable findings at 93 ppm were statistically significant decreases in final body weight (8.9% less than controls) in male rats and absolute spleen weight (20% less than controls) in male guinea pigs, indicating that the NOAEL and LOAEL for systemic effects are 49 and 93 ppm, respectively. In the reproductive toxicity study, male and female rats were exposed to 50, 150, or 394 ppm of 1,2-DCB for 6 hours/day, 7 days/week for 10 weeks before mating and subsequently through the F_1 generation (Bio/dynamics 1989). $\alpha_{2\mu}$-Globulin-related renal changes were found in adult males of both generations at all levels of exposure, but these effects are specific to male rats and are not relevant to humans. Decreased body weight gain, increased absolute and relative liver weights, and centrilobular hepatocyte hypertrophy occurred in adult rats of both sexes and generations at ≥150 ppm, indicating that the NOAEL and LOAEL for systemic effects are 50 and 150 ppm. There were no effects on reproduction in either generation, indicating that the NOAEL for reproductive toxicity is 394 ppm. As discussed in the acute inhalation MRL section, a NOAEL of 200 ppm and a LOAEL of 400 ppm were found for developmental toxicity (skeletal variations) in rats (Hayes et al. 1985).

As discussed above, NOAELs of 49–50 ppm and LOAELs of 93–150 ppm are identified for systemic effects in intermediate-duration inhalation studies of 1,2-DCB in rats and guinea pigs (Bio/dynamics 1989; Hollingsworth et al. 1958). Neither of these studies evaluated possible effects in the nasal cavity, a known sensitive target of 1,2-DCB based on acute data. As discussed in the acute inhalation MRL section, 64 ppm was a serious LOAEL for nasal olfactory lesions in rats intermittently exposed to 1,2-DCB for 4–14 days (Zissu 1995). Derivation of an intermediate-duration MRL for 1,2-DCB is precluded because the 64 ppm serious LOAEL for acute exposure is lower than the available intermediate-duration LOAELs for systemic and developmental effects.

No MRL was derived for chronic-duration inhalation exposure to 1,2-DCB due to a lack of chronic inhalation studies.

1,3-Dichlorobenzene. No MRLs were derived for inhalation exposure to 1,3-DCB due to a lack of acute-, intermediate-, and chronic-duration inhalation studies.

1,4-Dichlorobenzene.

- An MRL of 2 ppm has been derived for acute-duration (≤14 days) inhalation exposure to 1,4-DCB.

A limited amount of information is available on the toxicity of inhaled 1,4-DCB in humans. Case reports of people who inhaled 1,4-DCB provide indications that the liver and nervous system are systemic targets of inhalation toxicity in humans, but are limited by lack of adequate quantitative exposure information and/or verification that 1,4-DCB was the only factor associated with the effects (Cotter 1953; Miyai et al. 1988; Reygagne et al. 1992).

Periodic occupational health examinations of workers who were exposed to 1,4-DCB for an average of 4.75 years (range, 8 months–25 years) showed no cataracts or any other lens changes in the eyes, or effects on clinical indices (red blood cell count, total and differential white blood cell counts, hemoglobin, hematocrit, mean corpuscular volume, blood urea nitrogen, sedimentation rate, or urinalysis) attributable to exposure (Hollingsworth et al. 1956). The odor was found to be faint at 15–30 ppm and strong at 30–60 ppm. Painful irritation of the eyes and nose was usually experienced at 50–80 ppm, although the irritation threshold was higher (80–160 ppm) in workers acclimated to exposure. Concentrations above 160 ppm caused severe irritation and were considered intolerable to people not adapted to it. The odor and irritation properties are considered to be good warning properties that are expected to prevent excessive exposures, although the industrial experience indicates that it is possible for people to become sufficiently acclimated to tolerate high concentrations of the vapor (Hollingsworth et al. 1956).

Information on effects of acute-duration inhalation exposure to 1,4-DCB in animals is available from short-term systemic toxicity studies in rats and guinea pigs (Hollingsworth et al. 1956), a male reproduction study rats (Anderson and Hodge 1976), and developmental toxicity studies in rats and rabbits (Hayes et al. 1985; Hodge et al. 1977). In the systemic toxicity study, five rats of each sex and five guinea pigs of each sex were exposed to 175 ppm of 1,4-DCB for 7 hours/day, 5 days/week for 16 days (Hollingsworth et al. 1956). Mild histological effects of interstitial edema, congestion, and alveolar hemorrhage were observed in the lungs of male rats and female guinea pigs. The experimental design and report of this study have a number of deficiencies, such that reported observations provide only qualitative evidence of exposure-related respiratory effects. In the reproduction study (a dominant lethal test), a NOAEL of 450 ppm was identified for reproductive performance in male mice that were exposed for 6 hours/day for 5 days prior to weekly mating with unexposed females for 8 weeks (Anderson and Hodge 1976). No maternal or developmental toxicity occurred in rats that were exposed to 75–500 ppm for 6 hours/day on days 6–15 of gestation (Hodge et al. 1977), indicating that the highest NOAEL for reproductive effects in rats is 500 ppm. A developmental study in which rabbits were exposed to 100–800 ppm for 6 hours/day on gestation days 6–18 found evidence of fetotoxicity (a minor variation of the circulatory system) only at 800 ppm, which was also maternally toxic as shown by body weight loss early in gestation (Hayes et al. 1985), indicating that 800 ppm is a LOAEL for maternal and developmental effects in rabbits.

The lung is the most sensitive organ for inhaled 1,4-DCB in rats and guinea pigs exposed to 173 ppm (Hollingsworth et al. 1956) because the only effects observed in the reproductive and developmental studies were indications of maternal and fetotoxicity in rabbits at a much higher level of 800 ppm (Hayes et al. 1985). Support for the respiratory tract as a sensitive target for 1,4-DCB vapor in animals is provided by the induction of nasal lesions in rats intermittently exposed to levels as low as 75 ppm for 104 weeks in the study used to derive the chronic inhalation MRL for 1,4-DCB (Japan Bioassay Research Center 1995). Additionally, the animal data are consistent with the human experience indicating that occupational exposure to 1,4-DCB causes painful nose and eye irritation in the range of 15–160 ppm (Hollingsworth et al. 1956). The current Threshold Limit Value-Time Weighted Average (TLV-TWA) for 1,4-DCB of 10 ppm, which is intended to minimize the potential for eye irritation in exposed workers (ACGIH 2001), is largely based on the human findings of Hollingsworth et al. (1956).

As discussed above, eye and nose irritation are critical effects of acute inhalation exposure to 1,4-DCB in humans. Because odor detection is a warning property expected to prevent irritation caused by 1,4-DCB (Hollingsworth et al. 1956), the highest level at which an odor was detected that was simultaneously without irritant effects, 30 ppm, was designated a minimal LOAEL for irritation for the purposes of derivation of the MRL; the 15 ppm level was therefore designated a NOAEL for irritant effects. Using the NOAEL of 15 ppm for eye and nose irritation in humans, and applying a total uncertainty factor of 10 (for individual variability), an MRL of 2 ppm was derived for acute inhalation exposure to 1,4-DCB.

- An MRL of 0.1 ppm has been derived for intermediate-duration (15–364 days) inhalation exposure to 1,4-DCB.

Information on effects of intermediate-duration inhalation exposure to 1,4-DCB is available from a multispecies subchronic toxicity study (Hollingsworth et al. 1956) and a 2-generation reproductive/developmental toxicity study in rats (Tyl and Neeper-Bradley 1989). In the multispecies subchronic study, rats, mice, guinea pigs, rabbits, and monkeys were exposed to 96 or 158 ppm for 7 hours/day, 5 days/week for 5–7 months (Hollingsworth et al. 1956). Some of these animals were also similarly exposed to 341 ppm for 6 months (rats and guinea pigs) or 798 ppm for 23–69 exposures (rats, guinea pigs, and rabbits). The experiments with rabbits and monkeys exposed to levels of 96 or 158 ppm are limited by small numbers of animals (1–2/group). Hepatic effects included increased relative liver weight and slight histological alterations in rats at 158 ppm (not observed at 96 ppm), and more severe histopathology (e.g., cloudy swelling and necrosis) in guinea pigs at 341 ppm, and in rats, guinea pigs, and rabbits at 798 ppm. Other findings in the animals exposed to 798 ppm included eye irritation and frank signs of neurotoxicity (e.g., marked tremors). The hepatic histological changes observed in rats at 158 ppm (cloudy swelling, congestion, or granular degeneration) were considered of questionable significance and were not reported at 358 ppm, indicating that neither 158 nor 358 ppm is a reliable LOAEL for liver pathology in rats. The hepatic histological effects observed in the guinea pigs at 341 ppm appear to have been more severe (fatty degeneration, focal necrosis, slight cirrhosis) than in rats, but only occurred in some of the animals (number not reported). Although this information suggests that 341 ppm is a LOAEL for liver histopathology in guinea pigs, confidence in this effect level is low due to imprecise and brief qualitative reporting of the results (a general limitation of the study). The 798 ppm exposure concentration is a reliable LOAEL because this level clearly caused both liver histopathology (e.g., cloudy swelling and central necrosis) and overt signs of toxicity (e.g., marked tremors, eye irritation, and unconsciousness) in all three species.

The 2-generation study (Tyl and Neeper-Bradley 1989) is well-designed and identified a NOAEL (66 ppm, for a <10% change in absolute and relative liver weights) and LOAEL (211 ppm, for a >10% change in absolute and relative liver weights) for intermediate-duration inhalation exposure to 1,4-DCB. In this study, groups of 28 Sprague-Dawley rats of each sex were exposed to actual mean 1,4-DCB concentrations of 0, 66, 211, and 538 ppm. Additional groups of 10 females were similarly exposed for 10 weeks in a satellite study. The animals in the main study were paired within groups for a 3-week mating period to produce the F_1 generation. Main study males that did not successfully mate in the first 10 days of the mating period were paired with the satellite females for 10 days. Main study females that did not successfully mate during the first 10 days of the mating period were paired with proven males for the remaining 11 days of the mating period. Exposures of the main study F_0 females were continued throughout the mating period and the first 19 days of gestation, discontinued from gestation day 20 through postnatal day 4, and then resumed until sacrifice at weaning on postnatal day 28. Exposures of the satellite F_0 females were continued through mating until sacrifice on gestation day 15. Exposures of the F_0 males continued until sacrificed at the end of the study and satellite mating periods. Groups of 28 F_1 weanlings/sex and satellite groups of 10 F_1 female weanlings were exposed for 11 weeks and mated as described above to produce the F_2 generation. Additionally, 20 F_1 weanlings/sex from the control and high exposure groups served as recovery animals that were observed without exposure for 5 weeks prior to sacrifice. Complete necropsies were performed on all F_0 and F_1 adult (parental) animals, F_1 recovery animals, F_1 weanlings not used in the rest of the study, and F_2 weanlings, and histology was evaluated in the F_0 and F_1 parental animals. Histological examinations were conducted on the liver and kidneys in all groups and on selected other tissues (pituitary, vagina, uterus, ovaries, testes, epididymides, seminal vesicles, prostate, and tissues with gross lesions) in the control and high-exposure groups. The kidney evaluation included examination for the presence of $\alpha_{2\mu}$-globulin droplets. Additional end points evaluated in the parental generations included clinical observations, mortality, body weight, and food consumption. Mating and fertility indices were determined for F_0 and F_1 males and females, and gestational, live birth, postnatal survival (4-, 7-, 14-, 21-, and 28-day), and lactation indices were determined for the F_1 and F_2 litters.

No effects on reproductive parameters in either generation were reported, although systemic toxicity occurred at all dose levels in F_0 and F_1 adult rats (Tyl and Neeper-Bradley 1989). Hyaline droplet nephropathy was found in F_0 and F_1 adult males at ≥66 ppm. Manifestations of this male rat-specific renal syndrome included $\alpha_{2\mu}$-globulin accumulation and increased kidney weights at ≥66 ppm, and other characteristic histological changes at 538 ppm. Body weights and weight gains were significantly reduced in F_0 and F_1 adult males and F_1 adult females during the pre-breed exposure periods at 538 ppm. Absolute liver weights were increased in F_0 males by 6, 16, and 38% in the 66, 211, and 538 ppm groups, respectively; the differences were statistically significantly different from control in the 211 and 538 ppm groups. In F_0 females, absolute liver weights were increased by 9% in the 211 ppm animals, and 31% in the 538 ppm animals, but only the high-dose animals were statistically significant from controls. Similar changes were seen in relative liver weights of the F_0 generation, with respective increases of 5, 14, and 52% in the 66, 211, and 538 ppm males and 4, 9, and 31% in the 66, 211, and 538 ppm females; all groups of treated males, and the 211 and 538 ppm female groups, were statistically significantly different from controls. Relative liver weights were also significantly increased in F_1 adult males at ≥211 ppm and in F_1 adult females at 538 ppm. Hepatocellular hypertrophy was observed in the livers of F_0 and F_1 males and females at 538 ppm; no hepatic histological changes were induced at the lower exposure concentrations. Other effects also occurred in the F_0 and F_1 males and females at 538 ppm, indicating that there was a consistent pattern of adult toxicity at the high exposure level, including reduced food consumption and increased incidences of clinical signs (e.g., tremors, unkempt appearance, urine stains, salivation, and nasal and ocular discharges); these effects only sporadically occurred at 211 ppm. Other effects at 538 ppm included reduced gestational and lactational body weight gain, and postnatal toxicity, as evidenced by increased number of stillborn pups, reduced pup body weight, and reduced postnatal survival in F_1 and/or F_2 litters. This study identified: (1) a NOAEL of 66 ppm and LOAEL of 211 ppm for increased (>10% above controls) relative liver weight in adult rats, and (2) a serious LOAEL of 538 ppm for systemic toxicity (central nervous system and other clinical signs) in adult rats and developmental toxicity (increased stillbirths and perinatal mortality) in their offspring (Tyl and Neeper-Bradley 1989).

The NOAEL of 66 ppm for increased liver weight in rats (Tyl and Neeper-Bradley 1989) is used as the basis for an intermediate-duration inhalation MRL. Using EPA (1994k) inhalation reference concentration (RfC) methodology to determine the MRL, the 66 ppm NOAEL was first duration-adjusted for intermittent exposure, as follows:

$$\begin{aligned} NOAEL_{ADJ} &= (NOAEL)\ (hours/24\ hours)\ (days/7\ days) \\ &= (66\ ppm)\ (6/24)\ (5/7) \\ &= 11.8\ ppm \end{aligned}$$

1,4-DCB exhibited the effect outside of the respiratory tract and is treated as a category 3 gas for purposes of calculating the RfC. The human equivalent concentration (HEC) for extrarespiratory effects produced by a category 3 gas is calculated by multiplying the duration-adjusted NOAEL by the ratio of blood:gas partition coefficients ($H_{b/g}$) in animals and humans (EPA 1994k). $H_{b/g}$ values were not available for 1,4-DCB in rats and humans. Using a default value of 1 for the ratio of partition coefficients, the $NOAEL_{HEC}$ becomes 11.8 ppm, as follows:

$$\begin{aligned} NOAEL_{HEC} &= (NOAEL_{ADJ})\ x\ [(H_{b/g})_{RAT}\ /\ (H_{b/g})_{HUMAN}], \\ &= 11.8\ ppm\ x\ [1] = 11.8\ ppm \end{aligned}$$

The $NOAEL_{HEC}$ was divided by a total uncertainty factor of 100 to derive the MRL. This uncertainty factor is comprised of component factors of 10 for interspecies extrapolation, and 10 for human variability. Although the rat exposure concentration was adjusted to a human equivalent concentration (HEC), an uncertainty factor of 10 was still applied, because HEC calculation was based on an assumption of equivalent blood-gas partition coefficients, and not on actual data. Dividing the 11.8 ppm $NOAEL_{HEC}$ for increased liver weight in rats by the uncertainty factor of 100 yields an MRL of 0.1 ppm for intermediate-duration inhalation exposure to 1,4-DCB. As discussed in Appendix A, this MRL is consistent with an MRL of 0.2 ppm calculated using benchmark dose analysis of the liver weight data.

- An MRL of 0.02 ppm has been derived for chronic-duration (≥365 days) inhalation exposure to 1,4-DCB.

A limited amount of information is available on the long-term toxicity of inhaled 1,4-DCB in humans. Periodic occupational health examinations of workers who were exposed to 1,4-DCB for an average of 4.75 years (range, 8 months to 25 years) showed no changes in standard blood and urine indices (Hollingsworth et al. 1956). The odor was found to be faint at 15–30 ppm and strong at 30–60 ppm. Painful irritation of the eyes and nose was usually experienced at 50–80 ppm, although the irritation threshold was higher (80–160 ppm) in workers acclimated to exposure. Concentrations above 160 ppm caused severe irritation and were considered intolerable to people not adapted to it. Occasional examination of the eyes showed no cataracts or any other lens changes. The odor and irritation properties are considered to be fairly good warning properties that should prevent excessive exposures, although the industrial experience indicates that it is possible for people to become sufficiently acclimated to tolerate high concentrations of the vapor (Hollingsworth et al. 1956). The data from this study are inadequate for chronic MRL derivation due to poor characterization of long-term exposure levels, insufficient investigation of systemic health end points, and reporting and other study deficiencies. Although the available occupational data are insufficient for chronic MRL derivation, the eye and nose irritation findings in humans are consistent with nasal effects observed in chronically exposed animals, as discussed below.

Information on the chronic inhalation toxicity of 1,4-DCB in animals is available from two studies in rats and mice (Japan Bioassay Research Center 1995; Riley et al. 1980a, 1980b). In the Riley et al. (1980a, 1980b) studies, rats of both sexes and female mice were exposed to 75 or 500 ppm of 1,4-DCB for 5 hours/day, 5 days/week for up to 76 weeks (rats) or 57 weeks (mice), followed by 32 weeks (rats) or 18–19 weeks (mice) without exposure. There were no exposure-related histopathological changes in the nasal cavity or other tissues in either species. Liver and kidney weights were increased in rats of both sexes at 500 ppm, but the toxicological significance is questionable due to the negative histopathology findings and the lack of related clinical chemistry effects. Evaluation of the mouse data is limited by reporting insufficiencies in the available summary of the study.

In the Japan Bioassay Research Center (1995) study, groups of 50 male and female F344/DuCrj rats and 50 male and female Crj:BDF1 mice were exposed to 1,4-DCB in target concentrations of 0, 20, 75, or 300 ppm for 6 hours/day, 5 days/week for 104 weeks. Study end points included clinical signs and mortality, body weight (weekly for the first 13 weeks, and subsequently every 4 weeks), and hematology, blood biochemistry, and urinalysis indices (evaluated at end of study). Selected organ weight measurements (liver, kidneys, heart, lungs, spleen, adrenal, brain, testis, and ovary) and comprehensive gross pathology and histology evaluations were performed on all animals at the end of the study or at time of unscheduled death. No interim pathology examinations were performed. As summarized below, the chronic inhalation data identify a NOAEL of 20 ppm and a LOAEL of 75 ppm for dose-related eosinophilic changes in the olfactory epithelium in female rats and mineralization of the testis in male mice.

For rats, the actual mean chamber concentrations were 0, 19.8, 74.8, or 298.4 ppm over the duration of the study. The number of rats surviving to scheduled termination was significantly ($p \leq 0.05$) reduced at 300 ppm in males (Japan Bioassay Research Center 1995). Survival in the male rats was noticeably lower than controls beginning at approximately study week 80, and overall survival at 0, 20, 75, and 300 ppm was 66% (33/50), 68% (34/50), 58% (29/50), and 36% (18/50), respectively. There were no exposure-related decreases in survival in the female rats. Various other effects also occurred at 300 ppm, including changes in organ weights (liver in both sexes, kidneys in males) and hematological and blood biochemical indices (mean cell volume, total cholesterol, phospholipids, blood urea nitrogen, creatinine, and calcium in males; total protein, total bilirubin, blood urea nitrogen, and potassium in females), but a lack of both numerical data and statistical analyses precludes interpretations of significance for these end points. Additional findings included histopathological changes in the kidneys and nasal epithelia. The kidney lesions occurred only in male rats at 300 ppm and included significantly increased incidences of mineralization of the renal papilla and in hyperplasia of the urothelium. The nasal lesions mainly included increased incidences of eosinophilic changes in the olfactory epithelium (moderate or greater severity) in males at 300 ppm and females at ≥75 ppm. Incidences of this lesion at 0, 20, 75, and 300 ppm were 1/50, 2/50, 2/50, and 7/50 in males, and 28/50, 29/50, 39/50, and 47/50 in females. The increases were statistically significant ($p \leq 0.05$, Fisher's Exact Test performed by ATSDR) and there was a trend of increasing response with increasing dose in both sexes (Cochran-Armitage test, performed by ATSDR). Additionally observed were significantly increased incidences of eosinophilic changes of the respiratory epithelium and respiratory metaplasia in 300 ppm females, and an increase in mineralization of the renal papilla in 300 ppm males.

For mice, the actual mean chamber concentrations were 0, 19.9, 74.8, or 298.3 ppm over the duration of the study. Survival was slightly reduced in male mice at all levels of exposure, but the decreases were not significantly different from controls or significantly dose-related ($p > 0.05$, Fisher's Exact and Cochran-Armitage tests performed by ATSDR). Survival in exposed females was comparable to controls. Terminal body weights were reduced at 300 ppm in both males (≈10–15% less than controls, beginning at

study week 80) and females (≈7–10% less than controls, beginning at study week 84). Various other effects also occurred in the 300 ppm mice, including changes in organ weights (increased liver weights in both sexes, increased kidney and decreased ovary weights in females) and hematology and blood biochemical indices (total cholesterol, SGOT, SGPT, LDH, and AP in both sexes; platelet numbers, total protein, albumin, total cholesterol, blood urea nitrogen, and calcium in females), but a lack of reported numerical data and results of statistical analysis precludes interpretation of these end points. Additional findings included histopathological changes in liver and testes of males. The incidence of centrilobular hepatocellular hypertrophy was significantly increased in males at 300 ppm (0/49, 0/49, 0/50, and 34/49), and the incidence of mineralization of the testis was significantly increased in males at ≥75 ppm (27/49, 35/49, 42/50, and 41/49). No nonneoplastic histological changes were observed in female mice.
The chronic NOAELs of 19.8 ppm for nasal olfactory epithelial lesions in rats and 19.9 ppm for testicular mineralization in mice (Japan Bioassay Research Center 1995) were considered for MRL derivation. HECs were calculated using EPA (1994k) inhalation dosimetric adjustment methodology to determine which of these NOAELs is the most appropriate basis for the MRL. The animal NOAELs were first duration-adjusted for intermittent experimental exposure, as follows:

Rat: $NOAEL_{ADJ}$ = (NOAEL) (hours/24 hours) (days/7 days)
= (19.8 ppm) (6/24) (5/7)
= 3.54 ppm

Mouse: $NOAEL_{ADJ}$ = (NOAEL) (hours/24 hours) (days/7 days)
= (19.9 ppm) (6/24) (5/7)
= 3.55 ppm

For the olfactory epithelium changes in rats, 1,4-DCB was treated as a category 1 gas with effects in the extrathoracic region for purposes of calculating the HEC. Using EPA (1988e, 1994b) reference values, the regional gas deposition ratio (RGDR) was calculated as follows:

$$RGDR_{ET} = [(V_E/SA_{ET})_A/(V_E/SA_{ET})_H]$$
$$= (0.24\ m^3/day/15cm^2)/(20\ m^3/day/200cm^2)$$
$$= 0.16$$

where: $RGDR_{ET}$ = regional gas deposition ratio in the extrathoracic region
V_E = minute volume in rats $(V_E)_A$ or humans $(V_E)_H$
SA_{ET} = extrathoracic surface area in rats $(SA_{ET})_A$ or humans $(SA_{ET})_H$

The rat $NOAEL_{ADJ}$ was multiplied by the $RGDR_{ET}$ to yield a $NOAEL_{HEC}$ of 0.57 ppm, as follows:

$$\begin{aligned} NOAEL_{HEC} &= NOAEL_{ADJ} \times RGDR_{ET} \\ &= 3.54 \text{ ppm} \times 0.16 \\ &= 0.57 \text{ ppm} \end{aligned}$$

For the testicular lesions in mice, 1,4-DCB exhibited the effect outside of the respiratory tract and consequently is treated as a category 3 gas for purposes of calculating the HEC. The HEC for extrarespiratory effects produced by a category 3 gas is calculated by multiplying the duration-adjusted LOAEL by the ratio of blood:gas partition coefficients ($H_{b/g}$) in animals and humans (EPA 1994k). $H_{b/g}$ values were not available for 1,4-DCB in rats and humans. Using a default value of 1 for the ratio of partition coefficients, the $NOAEL_{HEC}$ is 3.55 ppm, as follows:

$$\begin{aligned} NOAEL_{HEC} &= (NOAEL_{ADJ}) \times [(H_{b/g})_{MOUSE} / (H_{b/g})_{HUMAN}], \\ &= 3.55 \text{ ppm} \times [1] = 3.55 \text{ ppm} \end{aligned}$$

As derived above, the HECs corresponding to the NOAELs for the nasal lesions in rats and testicular lesions in mice are 0.57 and 3.55 ppm, respectively. The lower of these $NOAEL_{HEC}$ values was selected as the basis for the MRL. The $NOAEL_{HEC}$ of 0.57 ppm for nasal effects in rats was divided by a total uncertainty factor of 30 to calculate the MRL. This uncertainty factor is comprised of component factors of 3 for interspecies extrapolation and 10 for human variability. A 3-fold uncertainty factor was used instead of a default 10-fold factor to extrapolate from rats to humans, because the dosimetry adjustment (i.e., calculation of the human equivalent exposure for time and concentration [$NOAEL_{HEC}$]) addresses one of the two areas of uncertainty encompassed in an interspecies extrapolation factor. The dosimetric adjustment addresses the pharmacokinetic component of the extrapolation factor, but the pharmaco-dynamic area of uncertainty remains as a partial factor for interspecies uncertainty. Dividing the 0.57 ppm $NOAEL_{HEC}$ by the uncertainty factor of 30 yields an MRL of 0.02 ppm for chronic-duration inhalation exposure to 1,4-DCB. As discussed in Appendix A, this MRL is consistent with an MRL of 0.01 ppm calculated using benchmark dose analysis of the rat nasal lesion incidence data.

Oral MRLs

1,2-Dichlorobenzene.

- An MRL of 0.8 mg/kg/day has been derived for acute-duration (≤14 days) oral exposure to 1,2-DCB.

Information on effects of acute oral exposure to sublethal doses of 1,2-DCB consists of findings in three systemic toxicity studies in rats and mice and one developmental toxicity study in rats (NTP 1985; Rimington and Ziegler 1963; Robinson et al. 1991; Ruddick et al. 1983). These studies administered the compound by gavage and collectively identify the liver as the most sensitive target. Severe liver damage, characterized by intense necrosis and fatty changes as well as porphyria, occurred in rats administered 455 mg/kg/day for 15 consecutive days (Rimington and Ziegler 1963). Rats that were exposed to 300 mg/kg/day for 10 consecutive days had hepatic effects that included necrosis and increased serum ALT (Robinson et al. 1991). Hepatocellular degeneration and necrosis occurred in mice that were exposed to 250 or 500 mg/kg/day for 14 consecutive days (NTP 1985). The 15-day rat and 14-day mouse studies are limited by small numbers of animals (3–5 per dose) and lack of a NOAEL due a single dose level (Rimington and Ziegler 1963) or lack of histopathology evaluations at doses lower than the LOAEL (NTP 1985). The 10-day study (Robinson et al. 1991) is the most appropriate basis for MRL derivation because it is well designed, included four dose levels, and provides dose-response data for several hepatic end points.

In the Robinson et al. (1991) study, groups of 10 male and 10 female Sprague-Dawley rats were treated with 1,2-DCB in corn oil by gavage at doses of 0, 37.5, 75, 150, or 300 mg/kg/day for 10 consecutive days. The doses were selected on the basis of a reported rat oral LD_{50} of 500 mg/kg. End points evaluated during the study included clinical signs, body weight, and food and water consumption. Evaluations at the end of the exposure period included hematology (5 indices), serum chemistry (9 indices including aspartate AST, ALT, LDH, cholesterol, blood urea nitrogen, and creatinine), and selected organ weights (brain, liver, spleen, lungs, thymus, kidneys, adrenal glands, heart, and testes or ovaries). Histological examinations were performed on various tissues including liver, kidneys, urinary bladder, heart, skin, muscle, bone, respiratory tract (nasal cavity with turbinates, lungs), nervous system (brain, sciatic nerve), immunological (spleen, thymus, lymph nodes), gastrointestinal (duodenum, ileum, jejunum, salivary gland, colon, cecum, rectum), endocrine (adrenal glands, pancreas), and reproductive (testes, seminal vesicles, prostate, ovaries) in the high-dose and control groups. Target organs identified in the high-dose group were also histologically evaluated at the lower dose levels.

No clinical signs or effects on survival were observed (Robinson et al. 1991). Body weight gain was significantly reduced in the male rats at 300 mg/kg/day (final body weights were 10.9% lower than controls), but not in females, and there were no exposure-related changes in food consumption in either sex. Statistically significant changes in organ weights predominantly occurred at 300 mg/kg/day, including significantly decreased absolute spleen weight in both sexes, and decreased absolute heart, kidney, thymus, and testes weights in males. Liver weight (relative and absolute) was significantly increased in females at ≥150 mg/kg/day and males at 300 mg/kg/day. Clinical chemistry findings included significantly increased serum ALT in both sexes at 300 mg/kg/day and serum phosphorus in females at ≥150 mg/kg/day. Serum cholesterol was significantly increased in females at ≥37.5 mg/kg/day, but the toxicological significance is unclear because the values were similar at all dose levels and showed no dose-response. Histopathological findings were limited to the liver and included necrosis that was slight in severity and significantly ($p=0.04$) increased in males at 300 mg/kg/day (4/10 compared to 0/10 in controls; incidences in other groups not reported but assumed to be 0/10). Incidences of other hepatic lesions were not significantly increased, but included inflammation (characterized by lymphocyte and macrophage infiltrates) and degeneration of hepatocytes (characterized by varying degrees of fibrillar or vacuolated cytoplasm and swelling with intact cell membranes). This study identified a NOAEL of 75 mg/kg/day and a minimal LOAEL of 150 mg/kg/day for increased liver weight in female rats, as well as a LOAEL of 300 mg/kg/day for liver necrosis in male rats.

The 75 mg/kg/day NOAEL for increased liver weight (Robinson et al. 1991) was used as the basis for the acute-duration oral MRL for 1,2-DCB. The NOAEL was divided by an uncertainty factor of 100 (10 for animal to human extrapolation and 10 for human variability) to derive an MRL of 0.8 mg/kg/day. As discussed in Appendix A, this MRL is consistent with an MRL of 0.4 mg/kg/day based on benchmark dose analysis of the liver weight data.

- An MRL of 0.4 mg/kg/day has been derived for intermediate-duration (15–364 days) oral exposure to 1,2-DCB.

Information on effects of intermediate-duration oral exposure to 1,2-DCB is available from three subchronic studies in rats and mice identifying the liver as the most sensitive target of toxicity (Hollingsworth et al. 1958; NTP 1985; Robinson et al. 1991). Incidences of degenerative liver lesions were significantly increased in rats exposed to 250–500 mg/kg/day for ≥13 weeks (Hollingsworth et al. 1958; NTP 1985; Robinson et al. 1991) and mice exposed to 250 mg/kg/day for 13 weeks (NTP 1985). Necrotic lesions occurred in several rats at 125 mg/kg/day (1/10 males, 3/10 females), but the increase was not statistically significant (NTP 1985). Other hepatic findings in rats exposed to lower doses (125–188 mg/kg/day for ≥13 weeks) included increases in relative liver weight and serum levels of ALT, cholesterol, serum protein, and decreases in serum triglycerides. Increased serum ALT is an inconsistent finding because it was induced in rats exposed to ≥100 mg/kg/day for 90 days (Robinson et al. 1991), but not in rats exposed to ≥125 mg/kg/day for 13 weeks (NTP 1985). Additionally, the increase in serum

ALT was not dose-related, and serum levels of other liver-associated enzymes were not increased in either the Robinson et al. (1991) study (AST, LDH, and AP) or the NTP (1985) study (AP and GGTP). The lowest LOAEL is 125 mg/kg/day, which is a minimal LOAEL for increased liver weight in rats in the NTP (1985) study.

In the NTP (1985) study, groups of 10 male and 10 female F344 rats and 10 male and 10 female B6C3F1 mice were administered 1,2-DCB in doses of 0, 30, 60, 125, 250, or 500 mg/kg/day for 5 days/week for 13 weeks. Histology examinations of the liver were limited to the control and three highest dose groups. Degenerative lesions were significantly ($p \leq 0.05$) increased in both species at ≥250 mg/kg/day. Changes in the rats included necrosis of individual hepatocytes at ≥250 mg/kg/day and centrilobular degeneration at 500 mg/kg/day; total incidences of these lesions at 0, 125, 250, and 500 mg/kg/day were 0/10, 1/10, 4/9, and 8/10 in males, and 0/10, 3/10, 5/10, and 7/8 in females. Relative liver weights were significantly increased 8, 17, and 45% in males in the 125, 250, and 500 mg/kg/day groups, respectively, and 8, 15, and 30% in females in the 125, 250, and 500 mg/kg/day groups, respectively; increased relative liver weights were not seen at lower doses of either sex. There were no increases in serum levels of liver enzymes [ALT, AP, or GGPT] at any dose in either sex. Serum cholesterol was significantly increased in males at ≥30 mg/kg/day (50.0, 17.6, 26.5, 70.6, and 109% higher than controls in the low to high dose groups; not significant at 60 mg/kg/day) and females at ≥125 mg/kg/day (12.2, 12.2, 32.6, 26.5, and 51.0%). Although increases in serum cholesterol were observed at doses as low as 30 mg/kg/day, the toxicological significance is unclear because there was no clear dose-response. Urinary concentrations of uroporphyrin and coproporphyrin were 3–5 times higher than controls in the 500 mg/kg/day males and females, but this increase was not considered indicative of porphyria because total porphyrin concentration in the liver was not altered at any dose level and no pigmentation indicative of porphyria was observed by ultraviolet light at necropsy. The 125 and 60 mg/kg/day doses are the LOAEL (minimal) and NOAEL, respectively, for hepatic effects in rats based on the increases in liver weight in both sexes.

In the mice, no compound-related histopathological changes were observed in either sex at 0 and 125 mg/kg/day or in females at 250 mg/kg/day. Lesions that were significantly increased included necrosis of individual hepatocytes, hepatocellular degeneration and/or pigment deposition in 4/10 males at 250 mg/kg/day, and centrilobular necrosis, necrosis of individual hepatocytes, and/or hepatocellular degeneration in 9/10 males and 9/10 females at 500 mg/kg/day. Relative liver weights were significantly increased at 500 mg/kg/day in both sexes, but there were no exposure-related changes in serum levels of

ALT, AP, or GGPT in either sex at any dose (no other clinical chemistry indices were examined in the mice).

The 60 mg/kg/day NOAEL for increased liver weight in rats (NTP 1985) was used as the basis for the MRL. The NOAEL was first adjusted for the intermittent experimental exposure (5 days/7 days) to give a duration-adjusted dose ($NOAEL_{ADJ}$) of 42.9 mg/kg/day. The $NOAEL_{ADJ}$ was divided by an uncertainty factor of 100 (10 for animal to human extrapolation and 10 for human variability) to derive an intermediate-duration oral MRL of 0.4 mg/kg/day for 1,2-DCB. As discussed in Appendix A, this MRL is consistent with an MRL of 0.2 mg/kg/day calculated using benchmark dose analysis of the rat liver lesion incidence data.

- An MRL of 0.4 mg/kg/day has been derived for chronic-duration (≥365 days) oral exposure to 1,2-DCB.

One chronic oral toxicity study of 1,2-DCB is available. In this study groups of F344/N rats (50/sex/group) and $B6C3F_1$ mice (50/sex/group) were administered 1,2-DCB in corn oil by gavage in doses of 0, 60, or 120 mg/kg/day for 5 days/week for 103 weeks (NTP 1985). Evaluations included clinical signs, body weight, and necropsy and histology on all animals. Organ weight and clinical chemistry indices were not assessed. The only exposure-related effect in either species was a significantly increased incidence of renal tubular regeneration in the male mice. This lesion showed a dose-related trend, and was statistically significantly elevated in high-dose animals, but not in low-dose animals. The NOAEL for the lesion was therefore 60 mg/kg/day, and the LOAEL was 120 mg/kg/day.

Because exposure occurred only 5 days/week, the NOAEL was duration-adjusted as follows:

$$
\begin{aligned}
NOAEL_{ADJ} &= \text{(NOAEL) (5 days/7 days)} \\
&= \text{(60 mg/kg/day) (5/7)} \\
&= \text{43 mg/kg/day}
\end{aligned}
$$

The MRL of 0.4 mg/kg/day was derived by dividing the $NOAEL_{ADJ}$ by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability). This value is consistent with an MRL of 0.3 mg/kg/day derived using benchmark dose analysis of the mouse kidney incidence data. It is noteworthy that the value of the chronic oral MRL is the same as that for the intermediate-duration MRL.

1,3-Dichlorobenzene.

- An MRL of 0.4 mg/kg/day has been derived for acute-duration (≤14 days) oral exposure to 1.3-DCB.

The acute oral database for 1,3-DCB consists of one short-term toxicity study in which groups of 10 male and 10 female Sprague Dawley rats were administered gavage doses of 0, 37, 147, 368, or 735 mg/kg/day in corn oil for 10 consecutive days (McCauley et al. 1995). End points evaluated during the study included clinical signs, survival, body weight, and food and water consumption. At the end of the study, blood was collected for hematology and serum chemistry analyses (erythrocytes, leukocytes, hemoglobin, hematocrit, mean corpuscular volume, glucose, BUN, creatinine, AP, AST, ALT, cholesterol, LDH, and calcium levels), and selected organs were weighed (brain, liver, spleen, lungs with lower half of trachea, thymus, kidneys, adrenal glands, heart, and gonads). Gross pathology was evaluated in all animals, and comprehensive histological examinations were performed in the high dose and control groups; histology in the lower dose groups was limited to the liver. Inflammatory and degenerative lesions were graded on a relative scale from one to four depending on the severity (minimal, mild, moderate, or marked).

No compound-related deaths or overt clinical signs were observed (McCauley et al. 1995). Body weight was significantly reduced in both sexes at 735 mg/kg/day (20 and 13% lower than controls in males and females, respectively). Food consumption was significantly decreased at 735 mg/kg/day in males (12%, normalized by body weight), and water consumption was significantly increased (8–13%) in females at ≥735 mg/kg/day. The hematological evaluation showed 8% decreased MCV in females at 735 mg/kg/day. The clinical chemistry analyses showed statistically significant changes in several indices, but serum cholesterol was the only end point that had values that exceeded the reference range. Serum cholesterol was significantly increased in females at 368 and 735 mg/kg/day (94 and 63% higher than controls, respectively), as well as in males at 368 and 735 mg/kg/day (79 and 84% higher than controls, respectively). Relative organ weight changes included significantly increased liver weight in males at ≥147 mg/kg/day and females at ≥368 mg/kg/day, decreased spleen weight in females at ≥368 mg/kg/day and males at 735 mg/kg/day, decreased thymus weight in both sexes at 735 mg/kg/day, and decreased testes weight in males at 735 mg/kg/day. Absolute organ weights were not reported. Histological changes primarily occurred in the liver, particularly centrilobular hepatocellular degeneration at ≥368 mg/kg/day. This lesion was characterized by varying degrees of cytoplasmic vacuolization and swelling with intact membranes, and occurred in the 368 and 735 mg/kg/day groups in 2/10 and 9/10 males, respectively, and 6/10 and 10/10 females, respectively; incidences in the other groups were not reported but are presumed to be 0/10. Other hepatic alterations included hepatocellular necrosis that was sporadically noted in the 147, 368, and 735 mg/kg/day groups. This change was usually minimal to mild, and was reported to increase in incidence and severity in the males in a dose-related manner; however, incidences were not reported. The only other reported histological change was atrophy of the thymus, characterized by loss of normal differentiation between medulla and cortex. The thymic atrophy was observed in 2/10 males (both marked in severity) and 2/9 females (both mild in severity) at 735 mg/kg/day; this change was not observed in controls, and the other dosed groups were not examined. The 147 mg/kg/day dose is the LOAEL (minimal) for liver effects based on the liver weight increase in male rats. The NOAEL for increased liver weight is 37 mg/kg/day.

The 37 mg/kg/day NOAEL for increased liver weight in rats (McCauley et al. 1995) was used as the basis for the MRL. The NOAEL was divided by an uncertainty factor of 100 (10 for animal to human extrapolation and 10 for human variability) to derive an intermediate-duration oral MRL of 0.4 mg/kg/day for 1,2-DCB. As discussed in Appendix A, benchmark dose analysis of the liver weight data yielded an MRL of 0.5 mg/kg/day.

- An MRL of 0.03 mg/kg/day has been derived for intermediate-duration (15–364 days) oral exposure to 1,3-DCB.

The database for intermediate-duration oral exposure to 1,3-DCB consists of one subchronic toxicity study in which groups of 10 male and 10 female Sprague Dawley rats were administered gavage doses of 0, 9, 37, 147, or 588 mg/kg/day in corn oil for 90 consecutive days (McCauley et al. 1995). End points evaluated during the study included clinical signs and mortality, body weight, and food and water consumption. At end of the exposure period, blood was collected for hematology and serum chemistry analyses (erythrocytes, leukocytes, hemoglobin, hematocrit, mean corpuscular volume, glucose, BUN, creatinine, AP, AST, ALT, cholesterol, LDH, and calcium levels), selected organs were weighed (brain, liver, spleen, lungs with lower half of trachea, thymus, kidneys, adrenal glands, heart, and gonads), and gross pathology was assessed. Histological examinations were performed on all tissues that were examined grossly in all high-dose rats and in one-half of control rats, as well as in the liver, thyroid, and pituitary glands from all animals in the 9, 37, and 147 mg/kg/day dose groups. Inflammatory and degenerative lesions were graded on a relative scale from one to four depending on the severity (minimal, mild, moderate, or marked).

No compound-related deaths or overt clinical signs were observed (McCauley et al. 1995). Body weight was reduced in both sexes at 588 mg/kg/day (24 and 10% lower than controls in males and females, respectively). The decreased weight gain was progressive throughout the exposure period and occurred despite increased food and water consumption in the same groups. Other effects included increased relative kidney weight in males at ≥147 mg/kg/day and females at 588 mg/kg/day, but there were no renal histopathological changes in any of the exposed animals. Hematological alterations consisted of significant increases in leukocyte levels in males at 147 mg/kg/day and females at 588 mg/kg/day, and in erythrocyte levels in males at 588 mg/kg/day. As discussed below, histopathology and serum chemistry findings indicated that the thyroid, pituitary, and liver were the most sensitive targets of toxicity.

Thyroid effects included significantly ($p \leq 0.05$) increased incidences of reduced colloidal density in follicles that exceeded normal variability in male rats at ≥9 mg/kg/day and female rats at ≥37 mg/kg/day (control to high dose group incidences of 2/10, 8/10, 10/10, 8/9, and 8/8 in males, and 1/10, 5/10, 8/10, 8/10, and 8/9 in females) (McCauley et al. 1995). Depletion of colloid density in the thyroid was characterized by decreased follicular size with scant colloid and follicles lined by cells that were cuboidal to columnar. The severity of the colloid density depletion generally ranged from mild to moderate, increased with dose level, and was greater in males than females. Incidences of male rats with thyroid colloidal density depletion of moderate or marked severity were significantly increased at ≥147 mg/kg/day (0/10, 0/10, 2/10, 5/9, and 6/8).

Pituitary effects included significantly ($p \leq 0.05$) increased incidences of cytoplasmic vacuolization in the pars distalis in male rats at ≥147 mg/kg/day (2/10, 6/10, 6/10, 10/10, and 7/7). The vacuoles were variably sized, irregularly shaped, and often poorly defined, and the severity of the lesions (*i.e.*, number of cells containing vacuoles) ranged from minimal to mild and generally increased with increasing dose level. Incidences of male rats with pituitary cytoplasmic vacuolization of moderate or marked severity were significantly increased at 588 mg/kg/day (1/10, 0/10, 2/10, 3/9, and 7/7). The pituitary lesion was reported to be similar to "castration cells" found in gonadectomized rats and considered to be an indicator of gonadal deficiency. No compound-related pituitary lesions were observed in female rats. Serum cholesterol was significantly increased in males at ≥9 mg/kg/day and in females at ≥37 mg/kg/day in a dose-related manner, and serum calcium was significantly increased in both sexes at ≥37 mg/kg/day. The investigators suggested that these serum chemistry changes might reflect a disruption of hormonal feedback mechanisms, or target organ effects on the pituitary, hypothalamus, and/or other endocrine organs.

Hepatic effects occurred in both sexes at 147 and 588 mg/kg/day, including significantly increased relative liver weight and incidences of liver lesions (McCauley et al. 1995). Absolute organ weights were not reported. Liver lesions were characterized by inflammation, hepatocellular alterations (eosinophilic homogeneous inclusions), and hepatocellular necrosis. Liver lesions that were significantly ($p \leq 0.05$) increased included hepatocellular cytoplasmic alterations of minimal to mild severity in males at ≥147 mg/kg/day (1/10, 2/10, 1/10, 6/10, and 7/9) and females at 588 mg/kg/day (0/10, 2/10, 0/10, 1/10, and 7/9), and necrotic hepatocyte foci of minimal severity at 588 mg/kg/day in both males (1/10, 2/10, 1/10, 2/10, and 5/9) and females (0/10, 0/10, 0/10, 3/10, and 5/9). Other statistically significant liver-associated effects included significantly increased serum AST levels (90–100% higher than controls) in males at ≥9 mg/kg/day and females at ≥37 mg/kg/day. Serum cholesterol levels were significantly increased in males at ≥9 mg/kg/day and females at ≥37 mg/kg/day, but might be pituitary-related, as indicated above. Serum LDH levels were reduced in males at ≥9 mg/kg/day and BUN levels were reduced in both sexes at 588 mg/kg/day, but the biological significance of decreases in these indices is unclear.

The lowest LOAEL in the McCauley et al. (1995) 90-day study is 9 mg/kg/day, which is the lowest tested dose and a minimal LOAEL for thyroid effects. The 9 mg/kg/day minimal LOAEL was used as the basis for the MRL. The LOAEL was divided by an uncertainty factor of 300 (3 for use of a minimal LOAEL, 10 for animal to human extrapolation, and 10 for human variability) to derive an intermediate-duration oral MRL of 0.03 mg/kg/day for 1,3-DCB. As discussed in Appendix A, benchmark dose analysis of the thyroid lesion incidence data also resulted in an MRL of 0.03 mg/kg/day.

No MRL was derived for chronic-duration oral exposure to 1,3-DCB due to a lack of chronic oral studies.

1,4-Dichlorobenzene. No acute-duration oral MRL was derived for 1,4-DCB due to insufficient data. Information on effects of non-lethal acute-duration oral exposures to 1,4-DCB is essentially limited to hepatic and renal changes of unclear toxicological significance observed in studies designed to elucidate mechanisms of liver and kidney toxicity in rats and mice. Acute liver damage, as assessed by histopathology and serum enzyme/biochemical indicators following gavage exposure, was not induced by high levels of 1,4-DCB in rat given single doses of ≤2790 mg/kg (Allis et al. 1992), rats and mice given single doses of ≤1,200 mg/kg/day (Eldridge et al. 1992), or rats and mice administered ≤300 and ≤600 mg/kg/day, respectively, 5 days/week for 1 week (Lake et al. 1997). Porphyria, manifested as increased porphyrin levels in liver and urine and suggestive of hepatic damage, was reported in rats that were orally exposed to 770 mg/kg/day for 5 days (Rimington and Ziegler 1963). Although there was no clear evidence of liver injury in acute studies, similar dose levels of 1,4-DCB are toxic following intermediate- and chronic-duration exposures.

Increased hepatocelluar proliferation, as measured by increased incorporation of bromodeoxyridine (BrdU) or [^{3}H]-thymidine into DNA-synthesizing liver cells, has been demonstrated in rats and mice at doses ≥150 mg/kg/day in a number of single dose and short-term oral studies that found no histological or other indications of overt liver damage (Eldridge et al. 1990, 1992; Hasmall et al. 1997; Lake et al. 1997; Sherman et al. 1998; Umemura et al. 1992, 1996). The induction of liver cell proliferation in the absence of manifest hepatoxicity suggests that the proliferation is a response to mitogenic stimulation rather than compensatory regeneration to cytotoxicity. Cellular proliferation and other changes have also been demonstrated in the kidney tubular epithelia of male rats, but not in female rats or mice of either sex, following short-term oral exposures to doses ≥150 mg/kg/day (Eldridge et al. 1992; Lake et al. 1997; Sherman et al. 1998; Umemura et al. 1992). The renal effects are consistent with the induction of $\alpha_{2\mu}$-globulin nephropathy in male rats by similar doses of 1,4-DCB in other acute oral studies (Charbonneau et al. 1989; Dietrich and Swenberg 1991; Saito et al. 1996), but are not relevant to humans. Induction of hepatic microsomal xenobiotic metabolizing enzymes appears to be the most sensitive effect of acute/short-term exposure to 1,4-DCB (Elovaara et al. 1998). For example, oral exposure to doses as low as 20 mg/kg/day for 14 days increased the activities of glucuronyl transferase, benzpyrene hydroxylase, and enzymes involved in the detoxification of O-ethyl-O-nitrophenyl phenylphosphorothionate (EPN) in rats (Carlson and Tardiff 1976). Induction of hepatic microsomal enzymes is not necessarily adverse, but does indicate that the liver is sensitive to relatively low doses of 1,4-DCB.

The toxicological significance of the hepatic microsomal enzyme changes is unclear and the information on other liver effects is insufficient to identify a reliable NOAEL or LOAEL for acute/short-term oral exposure to 1,4-DCB. The lack of adequate data on the threshold of adverse effects precludes derivation of an MRL for acute duration oral exposure.

- An MRL of 0.1 mg/kg/day has been derived for intermediate-duration (15–364 days) oral exposure to 1,4-DCB.

Information on the systemic toxicity of intermediate-duration oral exposure to 1,4-DCB is available from a number of studies conducted in rodents, mainly rats and mice, as well as one study in dogs. Liver and kidney effects are the most consistently observed, best characterized, and most sensitive findings in these studies. The lowest observed adverse effect level is for liver toxicity in dogs, although reproductive and developmental studies in rats indicate that offspring are particularly sensitive to 1,4-DCB toxicity during the postnatal preweaning period.

Hepatic effects induced by intermediate-duration oral exposures to 1,4-DCB ranged from increased liver weight and hepatocyte enlargement to hepatocellular degeneration, lesions, necrosis, and tumors in rats, mice, rabbits, and dogs. Increases in serum levels of enzymes and alterations in other end points (e.g., serum cholesterol and triglycerides) indicative of hepatocellular damage or liver dysfunction have also been induced. Increased liver weight is the most sensitive hepatic end point in subchronic studies in rats, observed at doses as low as 150 mg/kg/day for 4–13 weeks and 188 mg/kg/day for 192 days (Hollingsworth et al. 1956; Lake et al. 1997; Umemura et al. 1998). There was no indication of early liver damage in rats exposed to 150 mg/kg/day for 4 weeks using an immunohistochemical marker of centrilobular hepatocyte injury (Umemura et al. 1998), and increases in liver porphyrins in rats exposed to 50–200 mg/kg/day for 120 days were not considered to be toxicologically significant (Carlson 1977). Hepatocellular hypertrophy and decreased serum triglycerides occurred in rats exposed to ≥300 mg/kg/day for 13 weeks (Lake et al. 1997; NTP 1987). Higher dose levels of 1,4-DCB induced degenerative liver lesions in rats exposed to 376 mg/kg/day for 192 days (slight cirrhosis and focal necrosis) (Hollingsworth et al. 1956) or 1,200 mg/kg/day for 13 weeks (hepatocyte degeneration and necrosis) (NTP 1987). In mice, hepatocellular degeneration was induced at doses ≥600 mg/kg/day for 13 weeks (NTP 1987), and rabbits had cloudy swelling and minimal focal necrosis in the liver after exposure to 500 mg/kg/day for 367 days (Hollingsworth et al. 1956). Dogs are more sensitive to hepatic effects of 1,4-DCB than other species based on increases in liver weight, serum enzymes, and histopathology following exposure to doses as low as 50 mg/kg/day for 1 year (Naylor and Stout 1996).

Kidney effects, including collecting duct epithelial vacuolation, are additional effects of 1,4-DCB in dogs exposed to ≥50 mg/kg/day for 1 year (Naylor and Stout 1996). Renal changes, including hyaline droplet accumulation, increased kidney weights, and tubular lesions, are characteristically observed effects of subchronic and chronic oral exposure to 1,4-DCB in male rats at doses ≥75 mg/kg/day (Bomhard et al. 1988; Lake et al. 1997; NTP 1987). These findings are not considered for MRL derivation because there is a scientific consensus that they are related to the $\alpha_{2\mu}$-globulin nephropathy syndrome, which is specific to male rats and not relevant to humans. Subchronic studies in female rats found increased kidney weight, but no indications of nephrotoxic action (i.e., no histopathology or effects on urinary indices of renal function), following exposure to ≥188 mg/kg/day for 192 days or 600 mg/kg/day for 13 weeks (Bomhard et al. 1988; Hollingsworth et al. 1956).

Developmental toxicity studies provide no indications that 1,4-DCB is teratogenic in rats at oral doses as high as 1,000 mg/kg/day during gestation, although fetotoxicity occurred at maternally toxic levels ≥500 mg/kg/day (Giavini et al. 1986; Ruddick et al. 1983). Decreased maternal weight gain and increased incidences of extra ribs, a skeletal variation attributable to the maternal toxicity, occurred in rats at gestational dose levels ≥500 mg/kg/day, but not at 250 mg/kg/day (Giavini et al. 1986). In a 2-generation study, reproductive and developmental toxicity were evaluated in male and female rats that were orally exposed to 30, 90, or 270 mg/kg/day of 1,4-DCB (Bornatowicz et al. 1994). No effects on mating and fertility indices were observed at any level, although toxicity occurred in the offspring at doses ≥90 mg/kg/day. Effects at ≥90 mg/kg/day included reduced birth weight in F_1 pups and increased total number of deaths from birth to postnatal day 4 in F_1 and F_2 pups, clinical manifestations of dry and scaly skin (until approximately postnatal day 7) and tail constriction with occasional partial tail loss (during postnatal days 4–21) in F_1 and F_2 pups, reduced neurobehavioral performance (draw-up reflex evaluated at weaning) in F_2 pups, and increased relative liver weight in adult F_1 males. No exposure-related changes were found at 30 mg/kg/day, indicating that this is the NOAEL for reproductive and developmental toxicity in rats.

As discussed above, liver, kidney, and perinatal developmental toxicity are main effects of concern for intermediate-duration oral exposure to 1,4-DCB in animals. The dog is the most sensitive tested species, as liver and kidney effects were induced by exposure to doses as low as 50 mg/kg/day for 1 year (Naylor and Stout 1996), which is below subchronic LOAELs of approximately 150–200 mg/kg/day for these effects in rats and mice. The 2-generation study in rats demonstrates that oral exposure to 1,4-DCB can cause perinatal developmental toxicity, including reduced birth weight and neonatal survival in F_1 and F_2 pups, at doses ≥90 mg/kg/day (Bornatowicz et al. 1994). Although this finding indicates that perinatal developmental toxicity is an additional sensitive end point for 1,2-DCB exposure, the lower 50 mg/kg/day hepatotoxicity LOAEL in dogs (Naylor and Stout 1996) is a more appropriate basis for MRL derivation.

Information on the Naylor and Stout (1996) dog study was obtained from an EPA Data Evaluation Record summary of the original unpublished Monsanto Company report. In this study, groups of five male and five female Beagle dogs were orally administered 1,4-DCB by capsule at doses of 0, 10, 50, or 75 mg/kg/day for 1 year. Based on the summarized design of a 4-week dose range-finding study, it is presumed that dosing was 5 days/week. The 75 mg/kg/day dose is a time-weighted average reflecting dose decreases at the beginning of the study in response to unexpected severe toxicity. An initial high dose of 150 mg/kg/day was adjusted to 100 mg/kg/day for males during week 3, and a further decrease to 75 mg/kg/day was made for both sexes at the beginning of week 6. Both high dose males and females were untreated during weeks 4 and 5 to allow for recovery. Study end points included clinical observations, body weight, food consumption, ophthalmoscopic examination, hematology (11 indices, including activated partial thromboplastin time, at months 6 and 12), clinical chemistry (18 indices, including ALT, AST, GGTP, AP, and creatinine phosphokinase, at months 6 and 12), urinalysis (10 indices), organ weights, gross pathology, and histology.

Mortality occurred the first 25 days of the study before dose reduction; exposure to 150 mg/kg/day caused one male dog to be sacrificed in extremis on day 12, one male death on day 25, and one female death on day 24 (Naylor and Stout 1996). A control male died on day 83, but all other dogs survived to the end of the study. Treatment-related clinical signs were primarily limited to severely affected high-dose dogs and the control male that died; these included hypoactivity, dehydration, decreased defecation, blood-like fecal color, emesis, emaciation, and/or pale oral mucosa. There were no significant group differences in mean body weight at the end of the study. Body weight gain was significantly reduced during the first month of the study but recovered following dose reduction and adjustment of food availability. A mild anemia was observed at month 6 (significantly reduced red blood cells in females and HCT in males) at 75 mg/kg/day, but it resolved by the end of the study. The mild anemia correlated with histologic findings of bone marrow erythroid hyperplasia in females, and splenic excessive hematopoiesis and megakaryocyte proliferation in both sexes, indicating a compensatory response to the earlier anemia. Hepatic effects occurred at ≥50 mg/kg/day in both sexes as shown by changes in liver enzymes, increased liver weight, and histopathology. Effects on serum levels of enzymes included significantly increased AP (50 mg/kg/day males, and 50 and 75 mg/kg/day females, at months 6 and 12), ALT (75 mg/kg/day females at month 12), and gamma-glutamyltranspeptidase (GGTP) (75 mg/kg/day females at months 6 and 12), and significantly decreased albumin (50 and 75 mg/kg/day in males at months 6 and 12, and 75 mg/kg/day females at month 6). Absolute and relative liver weights were significantly increased in both sexes at 50 and 75 mg/kg/day (except absolute liver weight in 50 mg/kg/day males). Hepatic lesions included hepatocellular hypertrophy (all males and females at 50 and 75 mg/kg/day, and one female at 10 mg/kg/day), hepatocellular pigment deposition (two males and one female each at 50 and 75 mg/kg/day), bile duct/ductule hyperplasia (one male and one female at 75 mg/kg/day), and hepatic portal inflammation (periportal accumulation of neutrophils in an unspecified number of males at 50 and 75 mg/kg/day). Kidney effects included collecting duct epithelial vacuolation at 75 mg/kg/day in one male and at all dose levels in females (one each at 10 and 50 mg/kg/day and two at 75 mg/kg/day). The renal lesion was considered to be a possible effect of treatment at ≥50 mg/kg/day, because it was accompanied by increased relative kidney weight in females at ≥50 mg/kg/day and grossly observed renal discoloration in two females at 75 mg/kg/day.

The 50 mg/kg/day dose is the lowest LOAEL based on hepatic effects including increased liver weight, changes in liver enzymes, and histopathology. The NOAEL is 10 mg/kg/day and was used as the basis for the MRL. The NOAEL was duration-adjusted to 7.1 mg/kg/day [(10 mg/kg/day) x (5/7)], then divided by an uncertainty factor of 100 (10 for animal to human extrapolation and 10 for human variability) to derive an intermediate-duration oral MRL of 0.07 mg/kg/day for 1,4-DCB.

No MRL was derived for chronic-duration oral exposure to 1,4-DCB due to insufficient data. Information on the chronic oral effects of 1,4-DCB is available from one study each in rats, mice, and rabbits. Observed effects included nephropathy in rats (including tubular degeneration and atrophy in females) exposed to ≥150 mg/kg/day on 5 days/week for 103 weeks (NTP 1987), hepatocellular degeneration and nephropathy in mice exposed to ≥300 mg/kg/day on 5 days/week for 103 weeks (NTP 1987), and cloudy swelling and minimal focal necrosis in rabbits exposed to 500 mg/kg/day in 263 doses in 367 days (Hollingsworth et al. 1956). The lowest chronic LOAEL in these studies was 150 mg/kg/day for kidney effects in rats (NTP 1987). Derivation of a chronic oral MRL is precluded by the evidence for liver and kidney effects in dogs at doses as low as 50 mg/kg/day for 1 year in the less than chronic length study (Naylor and Stout 1996) used to derive the intermediate-duration MRL, suggesting that additional chronic data are necessary to identify an appropriate chronic NOAEL for use in MRL derivation.